

Role of polyunsaturated fatty acids in lung disease^{1,2}

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ABSTRACT DF Horrobin hypothesized that the low prevalence of lung disease among Eskimos is the result of their diet, which is high in n-3 fatty acids. The n-3 and n-6 fatty acids shunt eicosanoid production away from the arachidonic acid pathway, and hence decrease the production of bronchoconstrictive leukotrienes. Animal studies showed that eicosapentaenoic acid or γ -linolenic acid supplementation of animals exposed to endotoxins results in decreased effects on thromboxane B₂ and pulmonary vascular resistance. Small human trials confirmed that supplementation with eicosapentaenoic acid results in increased eicosapentaenoic acid in phospholipids and decreased generation of leukotrienes by neutrophils. Hence, a protective effect of such fatty acids in lung disease is biologically plausible. The results of human intervention studies looking at respiratory outcomes have been mixed, but they do suggest a possible difference between long-term and short-term effects. Epidemiologic studies showed possible protective effects against asthma in children, but weak to no evidence of such effects in adults. Results for bronchitis are more positive, although intervention trials are lacking. Recently, a cross-sectional analysis of data from the first National Health and Nutrition Examination Survey reported an \approx 80-mL difference in forced expiratory volume at 1 s between adults with high compared with low fish consumption. This response was not limited to asthmatic subjects. Others found that both fish consumption and n-3 fatty acid consumption (as estimated from food-frequency questionnaires) were protective against physician-diagnosed emphysema and chronic bronchitis and low spirometry values. Only smokers were included in this analysis. These results suggest that dietary fatty acids may play a role in lung disease; further work is needed to elucidate that role. *Am J Clin Nutr* 2000;71(suppl):393S-6S.

KEY WORDS Lung disease, diet, fish oil, n-3 fatty acids, polyunsaturated fatty acids, PUFAs, eicosapentaenoic acid, asthma, bronchitis

INTRODUCTION

In this article I review the evidence that dietary intakes of polyunsaturated fatty acids (PUFAs), primarily from diets rich in seafood, play a role in lung disease and in the normal aging process in the lung. First, however, I explain why it is plausible to study this relation at all.

It is well known that changes in dietary fatty acids can modulate inflammatory activity (1). Differences in fatty acid intakes translate into differences in the fatty acid content of lipid mem-

branes and other substrates (1, 2), which are in turn the substrates for eicosanoid production. Therefore, changes in the substrates can alter the distribution of the eicosanoids produced in the body. The presence of n-3 fatty acids lowers the production of inflammatory eicosanoids through competition with arachidonic acid as a constituent of lipid membranes, through competition with arachidonic acid as a substrate for prostaglandin-endoperoxide synthase (cyclooxygenase) activity, and through inhibition of the conversion of linoleic acid to arachidonic acid (1). γ -Linolenic acid has similar effects. The cyclooxygenase pathway, with arachidonic acid as a substrate, produces leukotriene B₄, which is a proinflammatory mediator and is responsible for neutrophil recruitment. It also produces leukotrienes associated with bronchoconstriction. When n-3 fatty acids are the substrate instead, less inflammatory mediators are produced. Hence, incorporation of n-3 fatty acids into lipid membranes and elsewhere may modulate inflammatory activity and bronchoconstriction.

The typical human lung has between 30 and 100 m² of exposed surface area. Because the function of the lung is gas exchange, the type of protection available to the skin is not feasible for this organ. Not surprisingly, inflammation is common in the lung. What is surprising is that in response to this inflammatory activity, fibrosis is rare. This contrasts with most other tissues in the body. Clearly, the lung has evolved mechanisms to protect itself; however, the evolutionary need for such mechanisms to function beyond child-rearing age is not clear. In any case, the human lung evolved during a period when the total intake of fatty acids and the distribution of types of dietary fatty acids were considerably different from those of today. This raises the question of whether the current mix and amount of fatty acid intake has consequences for the lung in health and disease.

Continuous inflammatory processes can take place in the lung. Continual smoking presents constant inflammatory stimuli to the lung. In addition, disease states such as asthma and bronchitis are characterized by continuous inflammation even in the absence of significant external stimulation. This inflammation appears to be critical to the disease process. For example, smoking cessation

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reduces the accelerated loss of lung function seen in smokers, and antiinflammatory agents (such as corticosteroids) that lower the underlying inflammation in asthma improve lung function and reduce the severity of symptoms in persons with asthma. Hence, it seems possible that factors that down-regulate inflammatory activity might be particularly useful in such diseases.

The beneficial effects of down-regulation may not be limited to persons with frank disease. Healthy persons who have never smoked lose ≈ 30 mL forced expiratory volume (FEV) per year of age because their lungs are constantly being challenged by both infectious agents and particles that elicit inflammatory responses, such as aeroallergens or combustion particles. These inflammations may be responsible for the gradual decline of lung function in those who have never smoked, although this hypothesis remains to be confirmed. Other factors, such as atopy in the absence of asthma, may put more stress on the antiinflammatory and repair mechanisms of the lung. As a result, a case can be made for why dietary intakes of PUFAs, if they indeed modulate eicosanoid activity in the lung, might both be protective against lung disease and ameliorate the normal decline in lung function with age. Having established that it is reasonable to study the relation between dietary PUFAs and both lung disease and the normal aging process in the lung, we can now examine the experimental findings.

ANIMAL STUDIES

Murray et al (3) examined a model of acute lung injury induced by an endotoxin. In pigs fed the control diet, lung injury resulted in a 10-fold increase in thromboxane B_2 production. Supplementation with fish oil (n-3 fatty acids) or borage oil (γ -linolenic acid) reduced the increase by a factor of 3. The increase in vascular pulmonary resistance and decrease in the partial pressure of oxygen and oxygen delivery with lung injury were also muted by PUFA supplementation.

Koch et al (4) studied perfused isolated rabbit lungs that were infused with fish oil, soy oil, or saline for 3 h and then challenged with an inflammatory stimulus. The lungs perfused with fish oil had significantly less edema than either those infused with saline or those infused with soy oil, with 50% less weight gain.

CLINICAL OBSERVATIONS

Several clinical observations have suggested that changes in fatty acid concentrations are associated with lung disease. For example, persons with cystic fibrosis have lower concentrations of essential fatty acids in their plasma lipids than do healthy control subjects (5-7). This is not to say that cystic fibrosis is produced by changes in fatty acids, but that the course of the disease may be influenced by those changes and related changes in eicosanoid production. Persons with atopy have also been reported to have lower ratios of n-3 to n-6 fatty acids in plasma lipids than healthy control subjects (8).

Small clinical trials

Asthmatic subjects

Treatment of asthmatic subjects with dietary PUFA supplements resulted in improved arachidonic acid concentrations in neutrophils, reduced neutrophil chemotaxis, reduced leukotriene generation (9, 10), and reduced airway late response to allergen exposure (11). These results are all consis-

tent with the proposed pathway by which dietary intake of PUFAs modulates lung disease, and they are all changes in intermediary biomarkers of the disease. However, no clinical improvement in asthmatic status was observed in these trials, with 2 exceptions (11-13). Dry and Vincent (14) supplemented their subjects (who were receiving inhaled steroids and nedocromil) with 1 g n-3 fatty acids/d for 1 y. The authors reported an increase in FEV at 1 s (FEV_1) of 23% after 9 mo of supplementation compared with an $\approx 10\%$ increase in the control group. Broughton et al (15) reported that a short course of n-3 fatty acid supplementation had no significant effect on baseline spirometry results, but did reduce methacholine responsiveness in a subset of subjects. That subset was defined by an increase in leukotriene E_5 excretion in response to the supplement.

The other clinical trials performed lasted from 1 to 6 mo, mostly <3 mo. For example, Thien et al (12) supplemented pollen-sensitive asthmatic subjects with 3.2 g eicosapentaenoic acid/d during 2 pollen seasons in London. No significant improvement in bronchial reactivity, symptoms, or peak expiratory flow was noted in this study. This raises the issue of whether the results reported by Dry and Vincent (14) and Broughton et al (15) were chance findings or whether the lack of clinical improvement in the other studies was the result of too short an intervention period or improvements restricted to a subset of subjects.

Cystic fibrosis subjects

Clinical trials in subjects with cystic fibrosis also showed that supplementation with PUFAs results in improvements in intermediate biomarkers of the disease. Again, the evidence for clinical improvement is weaker. A critical question is whether dietary changes in PUFA intake can result in changes in membrane phospholipids in cystic fibrosis subjects. Henderson et al (16) showed that this does occur. Given these changes, what happens to inflammatory eicosanoids? Kurlandsky et al (17) reported that leukotriene B_4 decreased, but there was no clinical improvement. Lawrence and Sorell (18) reported that supplementation with eicosapentaenoic acid restored neutrophil leukotriene B_4 receptors to normal in cystic fibrosis patients. Christophe et al (5, 6) reported that vital capacity was increased in cystic fibrosis patients supplemented with 1.5 g borage oil/d (which contained ≈ 330 mg γ -linolenic acid/d) compared with baseline.

Large observational studies

FEV₁

Sharp et al (19) examined the relation of FEV_1 with smoking and dietary fish consumption in the Honolulu Heart Study. This study included a significant number of men of Japanese descent who had relatively high fish intakes and therefore included a good range of exposure. High fish intake (twice a week or more) was associated with a 50-mL increase in FEV_1 in subjects currently smoking ≤ 30 cigarettes/d. An interaction with years of cigarette smoking and fish intake was also seen. The decline per additional year of smoking was lower in the group with high fish intake than in the group with low fish intake.

Schwartz and Weiss (20) also reported an association between FEV_1 and dietary fish consumption in the first National Health and Nutrition Examination Survey (NHANES I). High

fish consumption was associated with an ≈ 80 -mL increase in FEV₁ and this effect was not restricted to smokers.

Chronic obstructive pulmonary disease in adults

Schwartz and Weiss (21) examined subjects aged ≥ 30 y in NHANES II and reported a significant protective effect of dietary fish intake on chronic bronchitis (odds ratio = 0.74 for a 2-SD change). This association became insignificant, although still protective, after the authors controlled for dietary vitamin C and the dietary ratio of sodium to potassium.

Shahar et al (22) reported a dose-dependent decrease in risk of chronic obstructive pulmonary disease with increasing intake of n-3 fatty acids. In a reanalysis stimulated by the paper of Sharp et al (19), they also found an interaction with pack-years of smoking (number of packs of cigarettes smoked per day times the number of years smoked). The risk of an additional 10 pack-years declined in a dose-dependent manner with increasing intake of n-3 fatty acids.

In contrast, Miedema et al (23) reported the results of a 25-y prospective cohort study of the Zutphen cohort. They found no protective effect of n-3 fatty acids on chronic, nonspecific lung disease, a more inclusive category of lung disease that included emphysema and asthma as well as bronchitis.

Asthma in children

Two studies from Australia reported that dietary fish intake is protective against asthma prevalence in children. These studies are notable in that they did not depend solely on questionnaire data, but also included an assessment of airway responsiveness. Peat et al (24) found that children who ate fish more than once per week had lower rates of airway hyperresponsiveness than did children who ate fish less often. Hodge et al (25) reported that consumption of fresh fish, and particularly oily fish, was protective against wheeze and asthma. In contrast with these authors' earlier results, any fish consumption was not protective and fish consumption was not associated with hyperreactivity alone.

Asthma in adults

Schwartz and Weiss (21) reported that dietary fish intake was protective against frequent wheeze apart from colds (odds ratio = 0.82). However, control for vitamin C made that association insignificant. Troisi et al (26) examined the incidence of asthma in the Nurses' Health Study and found no significant association with dietary fish intake.

DISCUSSION

What are we to make of these findings? Several results are clear. Dietary changes in n-3 fatty acids do affect the composition of lipid membranes (1, 2), the production of eicosanoids, and neutrophil chemotaxis. Hence, there is clear evidence of an effect of n-3 fatty acids on potential modulators of lung disease.


Clinical intervention trials in persons with asthma, however, show little evidence of improvement in symptoms or in lung function, with the exception of the studies by Dry and Vincent (14) and Broughton et al (15). These results can be interpreted several ways. First, as Thien et al (27) noted, neutrophils play a less central role in asthma than in bronchitis, and little evidence has been found for changes in eosinophil or mast cell behavior in

response to changes in n-3 fatty acid intake. Hence, it is possible that the reduced inflammation resulting from n-3 fatty acid intake in persons with asthma is too small to result in clinical improvement. Alternatively, we must recognize that fish is a food, not a drug. As such, it may take more time for the smaller changes in inflammatory activity induced by fish consumption to result in improvement in symptoms or lung function. In this regard, cross-sectional studies, which presumably measure the effect of long-term diet on long-term prevalence of symptoms, may be better able to detect effects, unless clinical interventions are continued for ≥ 1 y as was done by Dry and Vincent (14). Given the greater potential for confounding in cross-sectional analyses, more long-term intervention trials seem the best approach to resolving this question.

It is also noteworthy that stronger evidence is seen for a protective effect against asthma in children than in adults. Given the small number of studies, this finding may be due to chance. However, the definition of an incident case of asthma in adults raises serious difficulties. Many cases of adult-onset asthma are actually the return of asthma symptoms in persons who had asthma in childhood. In the Nurses' Health Study (26), only the nurses' recollections of whether they had had asthma in early childhood were used to exclude these cases. Moreover, diagnostic patterns have changed considerably over time; in many children in whom asthma is now diagnosed, wheezy bronchitics would have been diagnosed in the 1950s. Hence, the outcome variable in the Nurses' Health Study is suspect.

Alternatively, childhood-incidence and adult-onset asthma may differ substantially. The immune system in adults, exposure scenarios, and other factors may make asthma in adults a somewhat different disease. In that case, it would be plausible that intake of a mild antiinflammatory agent might matter more in children, who have smaller airways. Again, the risk of overinterpreting the differences in the studies suggests that we need more data to resolve this issue.

The evidence for bronchitis is considerably stronger. The importance of neutrophil activity in this disease is unchallenged, and the epidemiologic data are much more consistent. There is still the possibility that dietary fish intake is merely a marker of good diet, but given the changes seen in intermediate markers of disease, a moderately good case exists for a role of dietary fish intake. In this regard it is interesting to note that wild game contains only 4% fat, compared with almost 25% fat in corn-fed beef. Hence, in prehistoric times, dietary intake of saturated animal fat was much lower than it is today. Dietary intake of linoleic acid would also have been quite low before the development of agriculture. Hence, it is likely that our species evolved during a time when fatty acids from fish were a larger constituent of total fatty acid intake than is true today.

Although all this evidence makes a good case, it does not yet make a convincing one. Too few studies exist to reliably judge consistency. Additionally, confounding by other dietary factors, particularly vitamin C, cannot be excluded. The findings discussed do suggest that this is a fruitful area for further work. Moreover, if it turns out that 2 portions of fish weekly convey some protection against the development of chronic lung disease, this would have substantial public health significance because such consumption is a plausible intervention. Furthermore, we are much more likely to be successful in encouraging such dietary change than we have been in, for example, motivating the general public to lose weight. 

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